Associations between Bladder Cancer Risk Factors and Tumor Stage and Grade at Diagnosis

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Using data on 1,860 bladder cancer cases and 3,934 population-based controls from the National Bladder Cancer Study, we examined associations between suspected bladder cancer risk factors and tumor stage and grade. Employment in a high-risk occupation was associated with the entire clinical spectrum of bladder cancer rather than a particular tumor stage or grade. For example, relative risks (RR) were similar for noninvasive and invasive disease (1.5 and 1.6, respectively). Cigarette smoking also increased risk of the entire clinical spectrum of bladder cancer, but the more advanced the stage, the stronger the effect. For example, relative risks of noninvasive and invasive bladder cancer for current heavy smokers were 3.0 and 5.2, respectively. Cigarette smoking was associated with higher risk of low-grade than high-grade tumors, once stage of disease was taken into account. Compared with whites, nonwhites were at a lower risk of noninvasive bladder cancer (RR = 0.4) but at similar risk of invasive bladder cancer (RR = 1.1), a pattern indicating racial differences in health practices related to bladder cancer detection. History of urinary tract infections and bladder stones was associated with increasing relative risks for advanced tumor stage. Heavy artificial sweetener use was associated with higher-grade, poorly differentiated tumors. Coffee consumption and family history of bladder cancer were not consistently associated with tumor stage or grade. Overall, different clinical presentations of bladder cancer share most suspected bladder cancer risk factors, including employment in a high-risk occupation and cigarette smoking. (Epidemiology 1994;5:218–225)

Keywords: grade, stage, bladder neoplasms, smoking, coffee, race, occupation, education, case-control study.

The prognosis of an individual with bladder cancer varies substantially according to the stage of the tumor at diagnosis. An estimated 70% of bladder cancer is diagnosed in a noninvasive stage.[1] The 5-year survival rate for individuals presenting with this form of bladder cancer is above 80%. In contrast, the 5-year survival rate for individuals diagnosed with invasive bladder cancer is less than 50%.[1] Tumor grade, reflecting tumor differentiation, is also an important prognostic indicator for bladder cancer. At every stage of disease, 5-year survival rates are higher for individuals with low-grade, well-differentiated tumors than for those with tumors that are high grade.[2]

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Submitted March 25, 1993; final version accepted June 30, 1993.

It has been suggested that etiologic factors, such as cigarette smoking and employment in high-risk occupations, may be differentially associated with bladder cancer severity. For example, there have been anecdotal reports that certain high-risk occupational exposures lead to more biologically aggressive tumors.[3–5] In addition, a recent study found that men employed in high-risk occupations were proportionately more likely to be diagnosed with high-grade tumors.[6] It has further been reported that younger men employed in high-risk occupations are more likely to be diagnosed with invasive than noninvasive bladder cancer.[6,7] Several studies also have shown that cigarette smokers compared with nonsmokers are more likely to be diagnosed with invasive than noninvasive tumors, and more likely to be diagnosed with high-grade than low-grade bladder tumors.[6,8]

In a large population-based, case-control study of bladder cancer, we collected data on the pathologic stage and grade of bladder cancer, along with information on suspected risk factors for bladder cancer, thus providing the opportunity to examine the possible influence of bladder cancer risk factors on grade and stage of disease. The present study has several advan-

tages over previous investigations of this topic, including a large number of cases and detailed assessment of a wide range of exposures.

Methods

Cases consisted of all residents of 10 geographic areas, ages 21–84, who were diagnosed with histologically confirmed bladder cancer over a 1-year period. The starting date varied across study areas from December 1977 to March 1978. Cases were identified through Surveillance, Epidemiology, and End Results (SEER) cancer registries in four states (Connecticut, Iowa, Utah, and New Mexico) and four metropolitan regions (Atlanta, Detroit, San Francisco, and Seattle) and through the New Jersey and New Orleans cancer registries.

Controls, randomly selected from the general population, were frequency matched to the age, sex, and geographic distribution of the cases. Telephone sampling of households was used to select controls age 21–64. Older controls were selected from Health Care Financing Administration records. Details of the study are described elsewhere.[9,10]

We interviewed 2,982 (73%) of the bladder cancer cases identified and 5,782 (83%) of the selected controls; 1,104 cases were not interviewed because of death (282), illness (288), patient refusal (252), doctor refusal (128), and other reasons (154), and a total of 1,203 selected controls were not interviewed because of death (101), illness (197), refusal (683), and other reasons (222). Structured personal interviews were conducted by trained personnel in the respondents' homes. In addition to obtaining data on sociodemographic factors and family history of urinary tract cancer, information was elicited about lifetime histories of tobacco use, employment, artificial sweetener use, and coffee intake. Data were also obtained about urinary tract infections and bladder stones that occurred more than 1 year before interview. Individuals were classified as ever having had a high-risk occupation according to results from previous analyses on this dataset.[11–13] Specifically, an occupation was considered to be at high risk if any of the following criteria was met: (1) an *a priori* suspect occupation with a relative risk in this study of ≥ 1.3; (2) any occupation with a relative risk in this study of ≥ 1.5; or (3) an occupation demonstrating a positive trend in risk with increasing number of years worked in this study (Appendix 1). For analyses designed specifically to examine the relation between high-risk occupation and grade or stage of bladder cancer, the analysis was limited only to men who had ever worked in a job for at least 6 months since the age of 12.

Data on stage and grade of bladder cancer at diagnosis were obtained from routinely collected cancer registry information. The present analysis is limited to data from the eight SEER registries that had standardized procedures to abstract clinical data from hospital charts and other medical records. A total of 1,030 cases and 1,848 controls from New Jersey and New Orleans were thus excluded. An additional 92 cases with a histologic type other than transitional cell carcinoma were excluded because of an earlier study suggesting that the etiology of bladder cancer varies by histology.[14] The final analytic dataset comprised 1,860 cases of transitional cell bladder cancer and 3,934 population controls.

Table 1 shows the percentage distribution of the cases by grade and stage. Over 60% of the cases were classified as noninvasive. The noninvasive category

TABLE 1. Distribution of Grade and Stage of Transitional Cell Bladder Cancer Cases (Eight SEER Regions)

Tumor Stage	Tumor Grade				Total (%)
	I	II	III/IV	Unknown	
Noninvasive	321	466	171	184	1,142 (61.3)
In situ	2	2	1	53	
Confined to mucosa	133	176	46	69	
Localized, NOS*	186	288	124	62	
Confined to submucosa	32	127	113	17	289 (15.5)
Muscle invasion	9	35	161	9	214 (11.5)
Extension beyond bladder	4	14	72	8	98 (5.3)
Unknown stage	14	29	18	56	117 (6.3)
Total (%)	380 (20.4)	671 (36.1)	535 (28.8)	274 (14.7)	1,860

* NOS = not otherwise specified.

included cases with *in situ* disease, cases with disease confined to the mucosa, and cases with localized disease. The decision to classify cases with localized disease as noninvasive was based on a pathologic re-review of cases from the Iowa cancer registry, in which more than 90% of the localized cases were found to have noninvasive cancer.[15] We excluded cases with unknown stage or grade from relevant analyses.

Separate unconditional logistic regression models were run with case-control status as the response variable for each grade and stage of bladder cancer to obtain relative risk estimates (RR) and 95% confidence intervals (CI).[16] The variables entered together into each model were age, race, education, sex, cigarette smoking, employment in a high-risk occupation, bladder stones, urinary infections, coffee consumption, family history of bladder cancer, and artificial sweetener use. Additional inclusion of geographic region in the models did not change the results presented in the tables.

Results

Stage of Bladder Cancer

Risks of each stage of bladder cancer increased with cigarette smoking, but the more advanced the stage, the higher the relative risk (Table 2). For example, individuals currently smoking 40 or more cigarettes per day faced a threefold risk of noninvasive disease,

TABLE 2. Relative Risk Estimates* of Transitional Cell Carcinoma of the Bladder by Tumor Stage for Suspected Bladder Cancer Risk Factors

				Invasive							
		Noninvasive		Overall		Confined to Submucosa		Invasion into Musculature		Extension beyond Bladder	
Risk Factor	Number of Controls	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Cigarette use											
Never	1,504	265	1.0	104	1.0	51	1.0	41	1.0	12	1.0
Ex-smoker (cigarettes/day)											
<20	471	121	1.5 (1.2–1.9)	53	1.6 (1.1–2.3)	23	1.5 (0.9–2.4)	18	1.3 (0.8–2.4)	12	2.9 (1.3–6.7)
≥20	740	224	1.6 (1.3–2.0)	141	2.6 (2.0–3.5)	74	2.8 (1.9–4.2)	42	2.0 (1.3–3.2)	25	3.8 (1.8–7.9)
Current smoker (cigarettes/day)											
<20	322	94	1.6 (1.2–2.1)	65	2.9 (2.1–4.1)	30	2.7 (1.7–4.3)	26	3.0 (1.8–5.0)	9	3.6 (1.5–8.9)
20–39	496	268	2.8 (2.2–3.4)	134	3.7 (2.8–4.9)	58	3.1 (2.0–4.7)	51	3.7 (2.4–5.8)	25	6.1 (2.9–12.9)
≥40	110	63	3.0 (2.1–4.2)	41	5.2 (3.4–8.1)	22	5.5 (3.1–9.7)	13	4.3 (2.2–8.5)	6	6.8 (2.4–19.4)
History of urinary infections											
None	3,336	908	1.0	482	1.0	241	1.0	172	1.0	69	1.0
1 or 2	343	113	1.3 (1.1–1.7)	61	1.4 (1.0–1.9)	27	1.2 (0.8–1.8)	23	1.4 (0.9–2.2)	11	1.9 (1.0–3.6)
≥3	205	104	2.1 (1.6–2.7)	49	1.9 (1.3–2.7)	18	1.3 (0.8–2.3)	17	1.9 (1.1–3.2)	14	4.6 (2.4–8.9)
History of bladder stones											
No	3,851	1,114	1.0	583	1.0	286	1.0	205	1.0	92	1.0
Yes	62	23	1.1 (0.7–1.9)	14	1.3 (0.7–2.5)	2	0.4 (0.1–1.7)	8	2.2 (1.0–4.8)	4	1.6 (0.5–4.8)
Artificial sweetener use (mg/day)											
<1,680	3,410	966	1.0	510	1.0	241	1.0	183	1.0	86	1.0
≥1,680	78	31	1.3 (0.9–2.1)	17	1.3 (0.8–2.3)	7	1.1 (0.5–2.5)	5	1.2 (0.5–3.0)	5	2.3 (0.9–6.0)
Coffee consumption (cups/week)											
<50	3,607	983	1.0	522	1.0	252	1.0	182	1.0	88	1.0
≥50	280	147	1.4 (1.1–1.7)	68	1.2 (0.9–1.6)	35	1.2 (0.8–1.8)	24	1.3 (0.8–2.1)	9	1.0 (0.5–2.1)
Family history of urinary tract cancer											
No	3,725	1,046	1.0	550	1.0	262	1.0	201	1.0	87	1.0
Yes	139	62	1.3 (1.1–1.7)	30	1.4 (1.0–1.9)	17	1.7 (1.0–3.0)	7	0.8 (0.4–1.9)	6	1.7 (0.7–4.1)
High-risk occupation†											
No	1,308	292	1.0	153	1.0	71	1.0	57	1.0	25	1.0
Yes	1,552	557	1.5 (1.3–1.8)	319	1.6 (1.3–2.0)	152	1.8 (1.3–2.4)	110	1.5 (1.1–2.1)	57	1.8 (1.1–2.9)
Race											
White	3,604	1,101	1.0	533	1.0	275	1.0	192	1.0	86	1.0
Nonwhite	330	41	0.4 (0.3–0.6)	48	1.1 (0.8–1.5)	14	0.7 (0.4–1.3)	22	1.4 (0.9–2.3)	12	1.4 (0.7–2.8)
Education (years)											
≥16	1,508	264	1.0	154	1.0	87	1.0	46	1.0	21	1.0
12–15	1,667	545	1.2 (1.0–1.4)	262	0.9 (0.8–1.2)	133	0.9 (0.7–1.2)	91	1.1 (0.8–1.6)	38	1.0 (0.6–1.8)
<12	1,209	333	1.1 (0.9–1.4)	185	1.0 (0.8–1.5)	69	0.7 (0.5–1.0)	77	1.3 (0.9–2.0)	39	1.4 (0.8–2.5)

* Adjusted for age, sex, and all other risk factors presented in table.
† Restricted to men with a complete occupational history.

rising to a sevenfold risk of metastatic disease. Similarly, the elevated risks seen among individuals reporting prior urinary tract infections or bladder stones also tended to rise with advancing stage. Heavy use of artificial sweeteners was also associated with a higher relative risk for metastatic disease.

By contrast, relative risks associated with heavy coffee intake, family history of urinary tract cancer, and employment in a high-risk occupation were similar across the different stages of bladder cancer. Relative risks associated with employment in individual high-risk occupations, including painters, motor vehicle drivers, railroad workers, hairdressers and barbers, petroleum processing workers, rubber processing workers, stationary engineers and firemen, blasters and powdermen, writers, and assessors and controllers, were also similar across the different stages of bladder cancer (data not shown).

To assess the effects of more recent occupational exposures on stage of disease, we examined the association between stage and employment in a high-risk occupation among men age 60 or younger. No consistent pattern was observed. Specifically, relative risks associated with a high-risk occupation were 1.5 (95% CI = 1.1–2.0), 3.4 (95% CI = 1.8–6.4), 1.1 (95% CI = 0.5–2.3), and 1.3 (95% CI = 0.4–4.3) for noninvasive disease, disease confined to the mucosa, disease invading into the musculature, and disease extending beyond the bladder, respectively.

Risk of noninvasive bladder cancer was lower among nonwhites than whites (RR = 0.4; 95% CI = 0.3–0.6), whereas risk of bladder cancer invading into muscle and beyond was elevated among nonwhites compared with whites. Risk of disease invading into muscle and beyond was also slightly elevated among those with less than a high school education.

Grade of Bladder Cancer

Grade of bladder cancer at diagnosis varied little according to cigarette smoking, prior urinary tract infections, family history of urinary tract cancer, and heavy coffee intake (Table 3). Individuals employed in high-risk occupations, including those employed in the individual occupations described above, were also at similarly elevated risk for each grade of bladder cancer. In addition, when the relation between grade and a high-risk occupation was examined among men age 60 or younger, risks were similarly elevated for each grade of bladder cancer. Specifically, risks associated with a high-risk occupation were 1.6 (95% CI = 1.0–2.5), 1.6 (95% CI = 1.1–2.4), and 1.4 (95% CI = 0.9–2.2) for grade I, II, and III disease, respectively.

Grade of bladder cancer at diagnosis did vary somewhat by bladder stones, artificial sweeteners, race, and education. Risk of low-grade but not high-grade disease was elevated among those with prior bladder stones. Risk of high-grade but not low-grade disease was increased among those with heavy artificial sweetener use. Risk of low-grade disease was higher among whites than nonwhites, whereas risk of high-grade disease was similar in both races. Risk of low-grade disease was inversely related to education, but risk of high-grade disease was unrelated to education.

Stage and Grade of Bladder Cancer

When the effects of stage and grade of disease were considered together (Table 4), two new patterns emerged. First, when the relation between cigarette use and grade of bladder cancer was examined separately for noninvasive and invasive disease, cigarette use was more strongly associated with low-grade than high-grade bladder cancer. Second, when the relation between artificial sweetener use and grade of bladder cancer was examined separately for noninvasive and invasive disease, heavy artificial sweetener use increased the risk of high-grade but not low-grade bladder cancer.

We examined the relation between cigarette smoking and tumor stage and grade according to age (<60 years, ≥60 years). In both age groups, risks associated with cigarette smoking were stronger for invasive than noninvasive bladder cancer. In addition, risks associated with cigarette smoking were stronger for low- than high-grade tumors, after taking stage of disease into account. Of interest, the relative risk of invasive bladder cancer associated with cigarette smoking was greater in the younger group, but the risk of noninvasive disease was similar in the two groups. For example, the relative risk of invasive, low-grade tumors associated with current heavy smoking was 11.5 (95% CI = 3.5–38.0) under age 60 *vs* 6.3 (95% CI = 2.7–14.7) at older ages.

Discussion

In a comparison of high-grade and low-grade bladder cancer cases reported to the Missouri cancer registry,[6] employment in a high-risk occupation was more strongly associated with high-grade tumors. In addition, employment in a high-risk occupation was more common among invasive than noninvasive bladder cancer cases in younger but not older men. In a recent small case-control study,[7] the relative risk was also higher for invasive than noninvasive bladder cancer among younger men occupationally exposed to aromatic amines, but the reverse was true among occu-

TABLE 3. Relative Risk Estimates* of Transitional Cell Carcinoma of the Bladder by Tumor Grade for Suspected Bladder Cancer Risk Factors

	Grade I		Grade II		Grade III/IV	
Risk Factor	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Cigarette use						
Never	78	1.0	127	1.0	118	1.0
Ex-smoker (cigarettes/day)						
<20	33	1.5 (1.0–2.4)	68	1.6 (1.2–2.2)	58	1.5 (1.1–2.1)
≥20	70	2.0 (1.4–2.9)	140	1.9 (1.5–2.5)	124	2.0 (1.5–2.7)
Current smoker (cigarettes/day)						
<20	37	2.2 (1.5–3.4)	63	2.2 (1.6–3.1)	49	1.9 (1.3–2.8)
20–39	105	4.0 (2.9–5.6)	159	3.2 (2.4–4.1)	112	2.7 (2.0–3.7)
≥40	23	4.1 (2.4–7.0)	44	4.1 (2.7–6.1)	26	2.9 (1.8–4.6)
History of urinary infections						
None	298	1.0	537	1.0	418	1.0
1 or 2	32	1.0 (0.7–1.5)	65	1.4 (1.0–1.9)	58	1.5 (1.1–2.0)
≥3	40	2.1 (1.4–3.2)	61	2.3 (1.6–3.2)	51	2.4 (1.7–3.4)
History of bladder stones						
No	364	1.0	657	1.0	520	1.0
Yes	13	2.0 (1.1–3.8)	12	1.0 (0.5–1.9)	12	1.1 (0.6–2.2)
Artificial sweetener use (mg/day)						
<1,680	324	1.0	522	1.0	453	1.0
≥1,680	9	1.1 (0.5–2.3)	16	1.1 (0.6–2.0)	23	2.2 (1.3–3.6)
Coffee consumption (cups/week)						
<50	326	1.0	578	1.0	562	1.0
≥50	49	1.3 (0.9–1.8)	87	1.3 (1.0–1.7)	61	1.4 (1.0–1.9)
Family history of urinary tract cancer						
No	346	1.0	611	1.0	492	1.0
Yes	23	1.7 (1.1–2.7)	38	1.6 (1.1–2.3)	27	1.4 (0.9–2.2)
High-risk occupation†						
No	92	1.0	167	1.0	143	1.0
Yes	170	1.4 (1.1–1.9)	360	1.7 (1.4–2.1)	277	1.5 (1.2–1.9)
Race						
White	363	1.0	652	1.0	490	1.0
Nonwhite	17	0.5 (0.3–0.9)	19	0.3 (0.2–0.6)	45	1.1 (0.8–1.6)
Education (years)						
≥16	74	1.0	169	1.0	132	1.0
12–15	194	1.5 (1.1–2.0)	323	1.1 (0.9–1.4)	227	1.0 (0.8–1.3)
<12	112	1.4 (1.0–2.0)	179	0.9 (0.7–1.2)	176	1.1 (0.8–1.4)

* Adjusted for age, race, and sex and all other risk factors presented in table.
† Restricted to men with a complete occupational history.

pationally exposed older men. The present study was able to examine the association between bladder cancer risk factors and severity of bladder cancer in over 1,700 bladder cancer cases and 3,934 controls from defined geographic areas using detailed data on a wide range of exposures and uniformly collected pathologic data. Contrary to anecdotal reports that occupationally induced bladder tumors are biologically aggressive,[3–5] we found that relative risks associated with employment in a high-risk occupation were similar for invasive and noninvasive disease and for high-grade and low-grade disease. We were unable, however, to examine specifically whether occupational exposure to human bladder carcinogens (that is, 2-naphthylamine, benzidine, 4-aminobiphenyl) is differentially associated with stage or grade of disease, because few men in our study were exposed to these substances.

Some,[6–8] but not all,[17–19] studies have found that bladder cancer among smokers is more often invasive than it is in nonsmokers. One study found this association to be present only among younger individuals.[7] Some,[8,17] but not all,[7,18,19] studies have also found

TABLE 4. Relative Risk Estimates* of Transitional Cell Carcinoma of the Bladder by Tumor Grade and Stage for Suspected Bladder Cancer Risk Factors

	Noninvasive				Invasive			
	Low Grade†		High Grade‡		Low Grade†		High Grade‡	
Risk Factor	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Cigarette use								
Never	165	1.0	52	1.0	30	1.0	64	1.0
Ex-smoker (cigarettes/day)								
<20	80	1.6 (1.2–2.2)	24	1.4 (0.8–2.3)	16	1.7 (0.9–3.2)	32	1.5 (1.0–2.4)
≥20	155	1.8 (1.4–2.3)	36	1.3 (0.8–2.0)	49	3.1 (1.9–5.0)	84	2.6 (1.8–3.7)
Current smoker (cigarettes/day)								
<20	61	1.7 (1.2–2.3)	14	1.3 (0.7–2.4)	29	4.5 (2.6–7.6)	33	2.3 (1.5–3.7)
20–39	205	3.3 (2.6–4.2)	29	1.7 (1.1–2.9)	53	5.0 (3.1–8.2)	77	3.5 (2.4–5.0)
≥40	48	3.5 (2.3–5.2)	4	1.1 (0.4–3.1)	17	7.9 (4.1–15.2)	22	4.6 (2.6–7.9)
History of urinary infections								
None	627	1.0	134	1.0	184	1.0	271	1.0
1 or 2	67	1.2 (0.9–1.6)	22	1.7 (1.1–2.8)	23	1.3 (0.8–2.1)	33	1.3 (0.9–2.0)
≥3	78	2.3 (1.7–3.1)	14	2.0 (1.1–3.7)	13	1.3 (0.7–2.3)	35	2.6 (1.7–3.9)
History of bladder stones								
No	766	1.0	168	1.0	215	1.0	334	1.0
Yes	17	1.2 (0.7–2.1)	3	0.7 (0.2–2.5)	5	1.4 (0.5–3.7)	9	1.4 (0.7–2.9)
Artificial sweetener use (mg/day)								
<1,680	668	1.0	146	1.0	188	1.0	293	1.0
≥1,680	19	1.1 (0.7–1.9)	9	3.0 (1.5–6.3)	4	0.8 (0.3–2.3)	13	1.7 (0.9–3.2)
Coffee consumption (cups/week)								
<50	668	1.0	156	1.0	197	1.0	293	1.0
≥50	109	1.4 (1.1–1.8)	15	1.3 (0.7–2.2)	23	1.0 (0.6–1.5)	43	1.4 (1.0–2.0)
Family history of bladder cancer								
No	714	1.0	158	1.0	202	1.0	318	1.0
Yes	48	1.7 (1.2–2.4)	7	1.1 (0.5–2.4)	11	1.4 (0.7–2.7)	19	1.6 (0.9–2.6)
High-risk occupation§								
No	192	1.0	50	1.0	53	1.0	89	1.0
Yes	392	1.6 (1.4–2.0)	82	1.4 (0.9–2.0)	120	1.8 (1.3–2.6)	185	1.6 (1.2–2.1)
Race								
White	763	1.0	164	1.0	211	1.0	310	1.0
Nonwhite	24	0.3 (0.2–0.5)	7	0.5 (0.2–1.0)	10	0.7 (0.3–1.3)	36	1.2 (0.8–1.8)
Education (years)								
≥16	168	1.0	45	1.0	63	1.0	85	1.0
12–15	392	1.4 (1.1–1.7)	70	0.9 (0.6–1.4)	102	0.9 (0.6–1.2)	147	1.0 (0.7–1.3)
<12	227	1.3 (1.0–1.6)	56	0.9 (0.6–1.5)	56	0.7 (0.5–1.1)	114	1.1 (0.8–1.5)

* Adjusted for age, race, and sex and all other risk factors presented in table.
† Grade I/II.
‡ Grade III/IV.
§ Restricted to men with a complete occupational history.

smokers more likely to be diagnosed with high-grade bladder cancer. We found that smokers were proportionately more likely than nonsmokers to be diagnosed with invasive disease, but not more likely to be diagnosed with high-grade tumors, as did Brooks and colleagues.[6] Our data suggest that, after taking into account stage of disease, smokers compared with nonsmokers were actually more likely to be diagnosed with low- than high-grade disease. A previous study has shown that cigarette smokers are somewhat less likely than nonsmokers to obtain medical care leading to early cancer detection, such as routine physical examinations, Papanicolaou smears, and mammography.[20] Thus, differential use of medical services by smoking status might explain why we found that smokers were proportionately more likely than nonsmokers to be

diagnosed with invasive bladder cancer. On the other hand, our data are also consistent with the hypothesis that certain compounds present in cigarette smoke act at a late stage in bladder cancer progression. An alternative explanation is that noninvasive and invasive disease are separate disease entities, with the latter being more strongly associated with cigarette smoking. The paradoxical observation that individuals who smoked were more likely, after stratification by stage of disease, to be diagnosed with low- than high-grade tumors needs to be confirmed in other investigations.

In this study, a prior history of bladder stones increased the risk of only the most advanced stages of bladder cancer. In addition, individuals with three or more urinary infections had a pronounced increase in risk of advanced bladder cancer, as previously described by Kantor and colleagues.[21] These findings suggest that bladder stones and urinary infections may represent complications of obstructive bladder cancer.

Analysis of the total dataset (3,010 cases and 5,783 controls) revealed a modest association between heavy use of artificial sweeteners and risk of bladder cancer,[9] but subsequent studies have not confirmed this association.[22] The observation in the present study that heavy users of artificial sweeteners were at particularly elevated risk of high-grade tumors was based on small numbers and needs to be examined in other studies.

Consistent with data from the Surveillance, Epidemiology, and End Results program,[23] we found that, compared with whites, nonwhites were more likely to be diagnosed with advanced stage disease but were less likely to be diagnosed with noninvasive disease. The subject of an earlier detailed report by Schairer and colleagues,[24] this observation suggests differential use of diagnostic services by race, with delay in obtaining medical attention among blacks. In light of the higher risk of all bladder cancer combined among whites compared with blacks, it also appears that whites, owing to increased medical surveillance, are more frequently diagnosed with conditions that as a group do not progress to invasive bladder cancer.

Misclassification of tumor stage and grade could result in an inability to detect clear etiologic entities in the clinical spectrum of bladder cancer. In fact, several problems in classifying bladder cancer on the part of both pathologists and cancer registry personnel have been documented.[15] First, it is not possible from the SEER registry data to separate reliably the two morphologic types of noninvasive bladder cancer: papillary transitional cell and flat transitional cell. Clinical series data indicate that flat lesions constitute less than 5% of noninvasive cases and have a poor prognosis. In contrast, the prognosis for the papillary lesions is thought to be good. We were unable to evaluate whether the risk factors are similar for these morphologically different types of bladder cancer. Second, the separation of noninvasive lesions from invasive lesions is also not straightforward. It is thus likely that a small portion of the noninvasive cases in this study are actually invasive and that the reverse is also true. The use of various grading schemes by pathologists, some based solely on the degree of tumor cell differentiation, with others based on additional factors, such as mitotic activity, could also be a source of misclassification.[2] A slide review of the pathologic tissue on the bladder cancer cases as part of the present study was not feasible, and thus our data should be interpreted with these limitations in mind.

The stages of bladder cancer at diagnosis may represent successive phases in the natural history of bladder cancer. If bladder cancer progresses from noninvasive to invasive disease, our data indicate that none of the established etiologic factors strongly influences this process. Alternatively, noninvasive disease may be a disease biologically distinct from invasive disease, as suggested by Raghavan *et al.*[25] Our data indicate that noninvasive and invasive bladder cancer share etiology—indeed, that bladder cancer at all stages and grades has similar etiology.

References

1. DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practices of Oncology. Philadelphia: JB Lippincott, 1985.
2. Henson DE. The histological grading of neoplasms. Arch Pathol Lab Med 1988;112:1091–1096.
3. Cartwright RA. Historical and modern epidemiological studies on populations exposed to N-substituted aryl compounds. Environ Health Perspect 1983;49:13–19.
4. Cartwright RA, Glashan RW, Grey B. Survival of transitional cell carcinoma cases in two Yorkshire centres. Br J Urol 1980;52:497–499.
5. Glashan RW, Wijesinghe DP, Riley A. The early changes in the development of bladder cancer in patients exposed to known industrial carcinogens. Br J Urol 1981;53:571–577.
6. Brooks DR, Geller AC, Chang J, Miller DR. Occupation, smoking, and the risk of high grade invasive bladder cancer in Missouri. Am J Ind Med 1992;21:699–713.
7. Hayes RB, Freidell GH, Hoar Zahm S, Cole P. Are the known bladder cancer risk factors associated with more advanced bladder cancer? Cancer Causes Control 1993;4:157–162.
8. Thompson IM, Peek M, Rodríguez FR. The impact of cigarette smoking on stage, grade and number of recurrences of transitional cell carcinoma of the bladder. J Urol 1987;137:401–403.
9. Hoover RN, Hartge Strasser P, Child MA, Mason TJ, Myers M, Silverman D, Altman R, Stemhagen A, Cantor K, Narayana A, Thomas D Key C, Sullivan JW, West D, Swanson GM, Meigs JW, Marrett LD. Artificial sweeteners and human bladder cancer: preliminary results. Lancet 1980;2:837–840.
10. Hartge P, Silverman D, Hoover R, Schairer C, Altman R, Austin D, Cantor K, Child M, Key C, Marrett LD, Mason TJ, Meigs JW, Myers MH, Narayana A, Sullivan JW, Swanson GM,

Thomas D, West D. Changing cigarette habits and bladder cancer risk: a case-control study. J Natl Cancer Inst 1987;78:1119-1125.
11. Silverman DT, Levin LI, Hoover RN, Hartge P. Occupational risks of bladder cancer in the United States. I. White men. J Natl Cancer Inst 1989;81:1472-1480.
12. Silverman DT, Levin LI, Hoover RN. Occupational risks of bladder cancer among white women in the United States. Am J Epidemiol 1990;132:453-461.
13. Silverman DT, Levin LI, Hoover RN. Occupational risks of bladder cancer in the United States. II. Nonwhite men. J Natl Cancer Inst 1989;81:1480-1483.
14. Kantor AF, Hartge P, Hoover RN, Fraumeni JF Jr. Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. Cancer Res 1988;48:3853-3855.
15. Lynch CF, Platz CE, Jones MP, Gazzaniga JM. Cancer registry problems in classifying invasive bladder cancer. J Natl Cancer Inst 1991;83:429-433.
16. Breslow NE, Day NE. Statistical Methods in Cancer Research. vol. 1. The Analysis of Case-Control Studies. IARC Scientific Pub. No. 32. Lyon: International Agency for Research on Cancer, 1980.
17. Carpenter AA. Clinical experience with transitional cell carcinoma of the bladder with special reference to smoking. J Urol 1989;141:527-528.
18. Morrison AS, Proppe KH, Verhoek WG, Aoki K, Leck I, Ohno Y, Obala K. Histology of bladder cancer. Manchester, UK and Nagoya, Japan. Int J Cancer 1982;30:701-705.
19. Jensen OM, Wahrendorf J, Blettner M, Knudsen JB, Sorenson BL. The Copenhagen case-control study of bladder cancer: role of smoking in invasive and noninvasive bladder tumours. J Epidemiol Community Health 1987;41:30-36.
20. U.S. Department of Health and Human Services. The Health Benefits of Smoking Cessation. DHHS Pub. No. (CDC)90-8416. Rockville, MD: U.S. Public Health Service, Office on Smoking and Health, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, 1990.
21. Kantor AF, Hartge P, Hoover RN, Narayana AS, Sullivan JW, Fraumeni JF Jr. Urinary tract infection and risk of bladder cancer. Am J Epidemiol 1984;119:510-515.
22. Silverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. Hematol Oncol Clin North Am 1992;6:15.
23. U.S. Department of Health and Human Services. Cancer Statistics Review, 1973-87. DHHS Pub. No. (NIH)90-2789. Bethesda, MD: U.S. Public Health Service, National Institutes of Health, National Cancer Institute, 1990.
24. Schairer C, Hartge P, Hoover RN, Silverman DT. Racial differences in bladder cancer risk: a case-control study. Am J Epidemiol 1988;128:1027-1037.
25. Raghavan, D, Shipley WU, Garnick MB, Russell PJ, Richie JP. Biology and management of bladder cancer. N Engl J Med 1990;322:1129-1137.

Appendix 1

Occupations considered high risk in this analysis include: boot blacks, painters, motor vehicle drivers, railroad workers, machinists, drill press operatives, stationary engineers and firemen, metal workers, hairdressers and barbers, asbestos workers, food service workers, construction workers, laborers, miscellaneous manufacturers, wood workers, agriculture technicians, gardeners, writers, telephone operators, assessors and controllers, architects, rubber processing workers, aluminum processing workers, petroleum workers, paper processing workers, gas station workers, auto workers, auto mechanics, dry cleaners, clerical workers, and police officers.